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HISTOPLASMOSIS INFECTION IN HUMAN—THE SILENT DISASTER

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ABSTRACT

Histoplasma capsulatum var. *capsulatum* and *Histoplasma capsulatum* var. *duboisii* and the human disease they cause, collectively referred to as histoplasmosis, are prevalent worldwide. *Histoplasmosis* is an opportunistic fungal infection caused by inhaling the spores of a fungus called Histoplasma capsulatum. The World Health Organization has officially recognised histoplasmosis as an AIDSdefining illness, a neglected tropical (fungal) disease, and an important cause of death in patients with advanced HIV disease. *Histoplasmosis* has an incredibly protean manifestation and is commonly misdiagnosed as tuberculosis or cancer. In the recent past, significant advancement has been achieved with respect to diagnostic and therapeutic approaches. Dr Samuel Darling was first described Histoplasmosis in 1906. *Histoplasma capsulatum* is a dimorphic fungus found in many parts of the world in soil enriched with bird droppings of certain birds and bats. *Histoplasma capsulatum* is a dimorphic fungus.

KEYWORDS: Dimorphic Fungus, Sabouraud's Agar, Epidemiology, Histoplasmosis, Itraconazole.

INTRODUCTION:
Histoplasmosis is a fungal infection caused by *Histoplasma capsulatum* [1]

Symptoms of this infection vary greatly, but the disease affects primarily the lungs [2]

Occasionally, other organs are affected; called disseminated histoplasmosis, it can be fatal if left untreated [3]

Histoplasmosis is common among AIDS patients because of their suppressed immunity [4]

Disseminated histoplasmosis is an AIDS-defining infection (and often referred to as progressive disseminated histoplasmosis), and co-infection with tuberculosis in AIDS patients presents further clinical challenges [5]

Other immunocompromised states also pose a risk including solid organ transplantation [6]

Recently collated older studies show the patchy distribution of Hcc in various areas around the world with case series in Brazil, South Africa ,and in India [7,8]

More recently, six new phylogenetic species, namely, LAm A1, LAm A2, LAm B1, LAm B2, RJ, and BAC-1, have been proposed existing within Latin America[9]

Majority of the immunocompetent individuals are asymptomatic, some develop self-limiting influenza-like syndromes [10,11]

As histoplasmosis was further characterized, it was understood to be intensely endemic in the Ohio and Mississippi River Valleys in the USA as well as in Central and South America [12]

Caves and chicken coops,decaying trees and riverbanks also make good habitats for incubations.[13]

Systemic spread usually occurs in patients with impaired cellular immunity [14]

Chronic progressive disseminated histoplasmosis has a long-term protracted course, lasting up to years, with long asymptomatic periods.[15]

HISTORY:
Travel or activities involving bats or birds, whether recent or remote, should aid in the differential [16]

Determine if the patient has a drug history or comorbid condition that is contributing to an immunocompromised state. The diagnosis of histoplasmosis should be considered in anyone with an acute febrile respiratory illness who has traveled to an area where histoplasmosis is endemic. Major extrapulmonary manifestations include pericarditis, rheumatologic symptoms, and ocular involvement.

DISTRIBUTION:
It is found in all parts of USA, especially in East Central states ,and less commonly in Latin America from Mexico to Argentina, In Europe, North and South East Africa, Nigeria, Malaysia, Indonesia and Australia.

SURFACE STRUCTURE OF *HISTOPLASMA CAPSULATUM:*
It is an oval, uninucleate, budding cell. It measures 2-4 microns.Growth does not occur above 37 degrees. In tissues the fungus is present inside phagocytic cells in the yeast phase. On Sabouraud's agar,white cottony mycelial growth appears, with large thick walled, spherical spores with tubercles or finger like projections. The appearance of the tuberculate spores is a diagnostic.

ANTIGENIC STRUCTURE:
After initial infection with histoplasma,persons have positive responses to skin tests, with histoplasmin, a filtrate of broth in which Histoplasma capsulatum has been grown. The reaction is delayed and tuberculin-like.Polysaccharides with precipitating and CF activity can be isolated from the yeast phase or mycelium. Cross reaction with blastomycin are significant.

INCEPTION OF INFECTION:
Histoplasmosis caused by *Histoplasma capsulatum* is primarily a disease of reticulo endothelial system. It is most frequently an asymptomatic ,self-limiting pulmonary infection, chronic or acute disseminated disease with poor prognosis may occur. Natural habitat of H*istoplasma capsulatum* is soil enriched with the dropping of birds or bats.Human infection results from inhalation of spores.Bats and many domestic animals ,such as cats and dogs are naturally infected with H*istoplasma capsulatum.*

SYMPTOMS:
A majority of the infections result in clinically insignificant respiratory disease or mild influenza-like illness. Some infections may cause acute pulmonary

histoplasmosis, manifested by dyspnea, hoarseness, cyanosis , night sweats, muscle/joint pain, weight loss, malaise, and flu-like symptoms, headache, cough, lymphadenopathy, caseating necrosis, fever, muscle pain, chest pain, Hepatomegaly, (coughing up blood),erythema nodosum.

Pestilential nature of *Histoplasma capsulatum:*
H capsulatum in the saprobic state grows in the mycelial form.

Susceptibility to dissemination is increased markedly with impaired cellular host defenses. Histoplasma infections are detected by the skin test. High degree of exposure to spores produce the skin lesions.the spores of histoplasma remains viable for years in the soil and and infectionis by inhalation of infected dust. Occasionally infection pases throughthe buccal or intestinal mucosa or through the skin. The disease attacks dogs, rats and mice,and then fungus multiplies in soil enriched by the droppings of chickens, pigeons and bats. The infection is hazard for exposures of caves. The parasite in yeast phase multiplies mainly in monocytes and macrophages and produces area of necrosis in which the parasites may abound. From blood they are carried to the liver, spleen and lymph nodes..

Acute pulmonary histoplasmosis:
Larger doses of spores, as from cleaning out old hen houses or exp loring bat-infested caves, lead benign pneumonitis. Pulmonary histoplasmosis may produce pathological changes similar to those of tuberculosis. It is an acute influenza like illness characterized by fever and non-productive cough. It is self limiting condition, and on recovery, patients are frequently left with discrete calcified area in the lung.

Chronic pulmonary disease:
It is mostly found in adults with formation of cavities in the lung either due to primary lesions or reactivation of apparently healed old lesion.clinical features resemble closely to that of pulmonary tuberculosis.Most of the pulmonary infections are benign producing no symptoms,but more severe infections may closely simulate pulmonary tuberculosis,including the production of a primary complex with enlarged satellite lymph nodes,multiple small discrete lesions and occasionally cavitation.Chronic cavitary histoplasmosis occurs most often in adult males.

Disseminated disease:
Severe disseminated disease develop in a small minority of infected individuals, particularly infants and aged or immunosuppressed individuals. the reticulo endothelial system is particularly involved with lymphadenopathy, enlarged spleen, and liver, high fever, anaemia, and a high mortality rate. Ulcers of the nose, mouth, tongue, and intestine can occur. In such individuals, the histologic lesion shows focal areas of necrosis in small granulomas in many organs. Phagocytic cells, contain a small ,oval yeast cells

The subacute form is associated with a wide spectrum of symptoms that may occur as a result of dissemination and subacute expression in the affected organs.[17]

COMPLICATIONS:
Acute respiratory distress syndrome. Histoplasmosis can damage lungs to the point that the air sacs begin filling with fluid. Heart problems. Inflammation of the sac that surrounds your heart (pericardium) is called pericarditis. Adrenal insufficiency and Meningitis. Mediastinal and hilar lymphadenopathies usually resolve.

Granulomatous inflammation causes extensive enlargement with caseating necrosis that may fibrose with progressive healing. [18]

Adrenal insufficiency develops in 5-10% of patients with subacute pulmonary disseminated histoplasmosis, regardless of treatment. [19]

Immunity to Histoplasma Capsulatum:
Little is known about the precise mechanism involved in immunity to fungal infections. Researchers discovered that fungal prostaglandins deactivate immune cells, preventing them from destroying the infection [20]

Most cases of *Histoplasma capsulatum,* infections are asymptomatic or show only fever and cough for a few days or weeks. Following initial infection with *Histoplasma capsulatum,* most persons appear to develop some degree of immunity. Immunosuppression may lead to dissemination. Infection is believed to confer long-lasting immunity, the most important component of wichth-1 mediated. In experimental infections macrophages activated by Tlymphocyte-derived cytokines are able to inhibit intracellular growth of *Histoplasma capsulatum* and thus control the disease. Neither B-cell nor antibody have a significant influence to reinfection [21]

In contrast to macrophages, human DCs rely on VLA5 for fungal recognition [22]

Differential recognition of H. capsulatum by macrophages and DCs may trigger unique signalling cascades. CD11b/CD18 triggers activation of the tyrosine kinase Syk and downstream production of proinflammatory cytokines in macrophages ([23]

Alveolar macrophages then engulf the fungi but can't destroy it either, but instead the yeast multiplies inside it . In immunocompetent individuals, T-cell-mediated immunity is activated, and the T-cells release pro-inflammatory cytokines which activate mononuclear phagocytes, hence producing tumour necrotic factor α (TNFα) and more cytokines.

CD11/CD18 blockade reduces, but does not prevent, *H. capsulatum* uptake by both human and murine macrophages.[24]

Differential recognition of *H. capsulatum* by macrophages and DCs may trigger unique signalling cascades. [25]

H. capsulatum may disseminate to other organs but on activation of cellular immunity, it is quickly controlled. [26]

T-cell-mediated immunity may not contain the infection, as poorly circumscribed granulomas are usually formed, and progressive dissemination may occur.[27]

Ancient science needs to be put to modern tests:
Fungal blood cultures are used for detection of blood stream infection caused by fungi,especially when dimorphic species and uncommon pathogens are suspected.Identification,susceptibility,and further testing can be performed on culture isolates.

Histoplasmosis poses a difficult diagnostic challenge because of its highly protean clinical manifestations. Being a primary pathogen, the etiologic agent, *H. capsulatum var capsulatum* infects the immunocompetent as well as immunocompromised patients. At room temperature (25–30°C) in the laboratory, *H. capsulatum var. capsulatum* appears as a slow growing mold, requiring 3–6 weeks for its cultivation. Although culture has been considered as the gold standard among the laboratory diagnostic tests, its value is limited by the fact that most of the diagnostic microbiology laboratories in t hospitals discard their cultures after 48–72 hours. Moreover, Sabouraud agar routinely used as a mycological medium is unsuitable for this fastidious fungal pathogen

DIRECT EXAMINATION:
Smears of sputum or pus are stained by Wright or Giemsa stains and examined microscopically.The smears are oval,packed within macrophages or monocytes. Blood smears may be positive particularly in patients suffering from AIDS.Specific immunofllurescence can identify the fungus.

CULTURE:
Specimens are cultured at 37 degrees on glucose-cysteine agar and on Sabouraud's agar. Culture must be kept for three weeks or more.Injection of the organism into mice may yield Histoplasma in lesions of spleen and liver upon culture.

ANIMAL INOCULATION:
Mice are susceptible to histoplasma infection. Clinical material,soil,faeces or culture is inoculated intraperitonially in mice. The spleen and liver are examined histologically and by culture after two weeks. or earlier on death of the animal.

SEROLOGY:
Latex agglutination, precipitation, and immunodiffusion tests become positive with in 2-4 weeks after infection. CF titers raise later in the disease,they fall to a very low levels if the disease is inactive.With progressive disease, the CF test remains positive in higy titer. CF antibody cross reacts with other fungal antigens.

A second-generation EIA was developed in 2004, which allowed for semi quantitative results, and a third-generation test (MiraVista *H. capsulatum* Galactomannan EIA) with greater specificity and quantitative results became available in 2007.

In contrast to the MiraVista assay, which requires processing in a central laboratory, an *in vitro* diagnostic EIA (IMMY ALPHA *Histoplasma* EIA) was approved by the Food and Drug Administration (FDA) on urine specimens in 2007 for use at local facilities. [28]

A subsequently developed analyte-specific reagent (ASR) *H. capsulatum* antigen EIA (IMMY) has shown improved performance characteristics , as well as high agreement with the MiraVista EIA [29]

MiraVista EIAs have shown increased sensitivity and an overall trend toward higher numerical values with the MiraVista EIAs [30]

Identification with the MALDI-TOF:
The identification of the colony can be carried out by matrix-assisted laser desorption/ionization time off light (MALDI-TOF [31,32])

DNA based detection methods PCR methods based on the detection of fungal DNA directly from clinical samples are currently implemented in the routine of

several laboratories for the diagnosis of main fungal infections, but there are considerably fewer PCR tests for the diagnosis of histoplasmosis. Their advantages rely on their simplicity, high specificity and short turnaround time with the bonus that real-time PCR (qPCR) formats allow for determining the fungal burden in patients by using non-specific DNA-binding dyes or fluorescently labeled probes [33]

However, this technique also has some limitations as the moderate amount of DNA in low invasive samples, the lack of standardization and the low availability of widely validated Commercial systems [34,35]

Breakthrough treatments and managements:
Specific treatment with amphotericin is indicated only in severe infections. If badly tolerated, the dosage may have to be reduced. Side effects are malaise, anorexia, nausea, fever, headache and venous thrombosis. These may be controlled to a considerable extent by the addition of 10 mg prednisolone to the intravenous solution. Plasma urea rises and haemoglobin falls during treatment, but later returns to normal.

Acute and moderate histoplasmosis:
Lipid AmB (3.5 mg/kg/day) Glucocorticoides for 1-2 weeks; then itraconazole (200mg) for 12 weeks

Chronic pulmonary/cavitory pulmonary histoplasmosis----
Itraconazole (200mg) for 12 weeks

Disseminated histoplasmosis—
Lipid AmB (3.5 mg/kg/day) for 1-2 weeks, then itraconazole (200mg) for 12 weeks

CNS histoplasmosis
Lipid AmB (5 mg/kg/day),4-6 weeks, then itraconazole (200mg) for 12 months.

Control:
Histoplasma grows more in soil mixed with bird /bat feces.Exposure in suchplaces may result in massive infection. In endemic area, smallinfective inoculate are spread by dust. Large number become infected early in,but without symptoms. Avoid exposure. Avoid projects and activities that might expose you to the fungus, such as cave exploring and raising birds, such as pigeons or chickens. Shower contaminated surfaces, and wear a respirator mask.

An opinion arrived at through a process of reasoning
Bacterial pneumonia,and Pulmonary histoplasmosis show similar clinical symptoms. imaging manifestations, bronchoscopy or CT-guided lung needle aspiration biopsy should be actively performed to clear the way for differential diagnosis of pulmonary infection, and later successfully treated with antifungal therapy. In a minority of cases the manifestations can mimic primary or metastatic malignancies leading to delay in appropriate treatment.

REFERENCES:

I. Johnstone, Ronald B. (2017). "25. Mycoses and Algal infections". Weedon's Skin Pathology Essentials (2nd ed.). Elsevier. p. 452

II. Stenn F (February 1960). "Cave disease or speleonosis". Archives of Internal Medicine. 105 (2): 181–3. .

III. Ryan KJ, Ray CG, eds. (2004). Sherris Medical Microbiology (4th ed.). McGraw Hill. pp. 674

IV. 4.Cotran RS, Kumar V, Fausto N, Robbins SL, Abbas AK (2005). Robbins and Cotran Pathologic Basis of Disease. St. Louis: Elsevier/Saunders. pp. 754–5.

V. Couppie P, Aznar C, Carme B, et al. . American histoplasmosis in developing countries with a special focus on patients with HIV: diagnosis, treatment, and prognosis. Curr Opin Infect Dis. 2006;19(5):443–449.

VI. Nieto-Rios JF, Serna-Higuita LM, Guzman-Luna CE, et al. . Histoplasmosis in renal transplant patients in an endemic area at a reference hospital in Medellin, Colombia. Transplant Proc. 2014;46(9):3004–3009.

VII. Bahr NC, Antinori S, Wheat LJ, et al. . Histoplasmosis infections worldwide: thinking outside of the Ohio river valley. Curr Trop Med Rep. 2015;2(2):70–80. doi: 10.1007/s40475-015-0044-0

VIII. Randhawa HS, Gugnani HC.. Occurrence of histoplasmosis in the Indian Subcontinent: An Overview and Update. J Med Res Pract. 2018;7:71–83.

IX. Teixeira Mde M, Patan ´e JS, Taylor ML, G ´omez BL, Theodoro RC, de Hoog S, Engelthaler DM, Zancop ´e-Oliveira RM, Felipe MS, Barker BM, 2016. Worldwide phylogenetic distributions and population dynamics of the genus Histoplasma. PLoS Negl Trop Dis 10: e0004732.

X. Myint T, Leedy N, Villacorta Cari E, Wheat LJ. HIV-associated histoplasmosis: Current perspectives. HIV/AIDS - Research and Palliative Care. 2020;12:113-125. Available from: https://www.dovepress.com/ hiv-associated-histoplasmosis-currentperspectives-peer-reviewed-article-HIV

XI. Vergidis P, Avery RK, Wheat LJ, Dotson JL, Assi MA, Antoun SA, et al. Histoplasmosis complicating tumor necrosis factor–α blocker therapy: A retrospective analysis of 98 cases. Clinical Infectious Diseases. 2015;61(3):409-417.

XII. Wheat LJ, et al. Histoplasmosis. Infect Dis Clin North Am. 2016;30(1):207–27

XIII. Ariffin A, Jagpal SK, Johannes J, Nagella N. Infections. Le T, Khosa S, Pasnick S, Wang T, eds. ATS Review for the Pulmonary Boards. 1st ed. New York, NY: American Thoracic Society; 2015. 469-72

XIV. Ferguson-Paul K, Park C, Childress S, Arnold S, Ault B, Bagga B. Disseminated histoplasmosis in pediatric kidney transplant recipients-A report of six cases and review of the literature. Pediatr Transplant. 2018 Nov. 22 (7):e13274

XV. Tanveer F, Younas M, Johnson LB. Chronic progressive disseminated histoplasmosis in a renal transplant recipient. Med Mycol Case Rep. 2019 Mar. 23:53-54.

XVI. Deepe GS Jr. Outbreaks of histoplasmosis: The spores set sail. PLoS Pathog. 2018 Sep. 14 (9):e1007213.

XVII. Kauffman CA. Histoplasmosis: a clinical and laboratory update. Clin Microbiol Rev. 2007 Jan. 20(1):115-32.

XVIII. Jazeela Fayyaz, Histoplasmosis,Medscape,2020

XIX. Hage CA, Wheat LJ, Loyd J, Allen SD, Blue D, Knox KS. Pulmonary histoplasmosis. Semin Respir Crit Care Med. 2008 Apr. 29(2):151-65

XX. Raghavendra Rao MV1* , Abrar A Khan2 , Srinivasa Rao D3 , Dilip Mathai4 , Mohammad Khaleel5 , Mubasheer Ali, How Fungus Can Debilitate Your Immune System?, Journal of Clinical Immunology & Microbiology, Volume 2; Issue 1 (2021) | JCIM-2(10)-017 |

XXI. Lin JS, Huang JH, Hung LY, Wu SY, Wu-Hsieh BA. Distinct roles of complement receptor 3, Dectin-1, and sialic acids in murine macrophage interaction with Histoplasma yeast. J Leukocyte Biol. 2010;88(1):95-106.

XXII.] Cáceres DH, Samayoa BE, Medina NG, Tobón AM, Guzmán BJ, Mercado D, et al. Multicenter validation of commercial antigenuria reagents to diagnose progressive disseminated histoplasmosis in people living with HIV/AIDS in two Latin American countries. The Journal of Clinical Microbiology. 2018;56(6):e01959-17

XXIII. Patra S, Nimitha P, Kaul S, Valakkada J, Verma KK, Ramam M, et al. Primary cutaneous histoplasmosis in an immunocompetent patient presenting with severe pruritus. Indian Journal of Dermatology, Venereology and Leprology. 2018;84:465-468

XXIV. Jawetz E, Melnick JL, Edelberg EA. A Lange medical book review of medical microbiology. 7th Ed.

XXV. Ivan Roitt M, Jonathan Brostoff, David Male K. Immunology. 2nd Ed.

XXVI. Philips CA, Augustine P, Kumar L, Mahadevan P. Addison's darling crisis. Indian Journal of Pathology & Microbiology. 2017;60:612-613

XXVII. Pujari A, Rakheja V, Bajaj M, Sen S, Yadav B. Isolated conjunctival histoplasmosis in an elderly patient: A rare but important scenario. Canadian Journal of Ophthalmology. 2019;54:e15-e16

XXVIII. Zhang X, Gibson B Jr, Daly TM. 2013. Evaluation of commercially available reagents for diagnosis of histoplasmosis infection in immunocompromised patients. J Clin Microbiol 51:4095–4101. doi:10.1128/JCM.02298-13.

XXIX. . Zhang C, Lei GS, Lee CH, Hage CA. 2015. Evaluation of two new enzyme immunoassay reagents for diagnosis of histoplasmosis in a cohort of clinically characterized patients. Med Mycol 53:868–873. doi:10.1093/mmy/myv062.

XXX. Theel ES, Jespersen DJ, Harring J, Mandrekar J, Binnicker MJ. 2013. Evaluation of an enzyme immunoassay for detection of Histoplasma capsulatum antigen from urine specimens. J Clin Microbiol 51:3555–3559. doi:10.1128/JCM.01868-13

XXXI. Campoy S, Adrio JL. Antifungals. Biochemical Pharmacology. 2017;133: 86-96.

XXXII. Kauffman CA. Histoplasmosis. Clinics in Chest Medicine. 2009;30(2):217-225

XXXIII. Manabe YC, Campbell JD, Sydnor E, Moore RD. Immune reconstitution inflammatory syndrome: 79 Treatment of Histoplasmosis DOI: http://dx.doi.org/10.5772/intechopen.92984 Risk factors and treatment implications. Journal of Acquired Immune Deficiency Syndromes. 2007;46(4):456-462

XXXIV. Kiggundu R, Nabeta HW, Okia R, Rhein J, Lukande R. Unmasking histoplasmosis immune reconstitution inflammatory syndrome in a patient recently started on antiretroviral therapy. Autopsy & Case Reports. 2016;6(4):27-33

XXXV. Passos L, Talhari C, Santos M, Ribeiro-Rodrigues R, Ferreira LC de L, Talhari S. Histoplasmosis-associated immune reconstitution inflammatory syndrome. Anais Brasileiros de Dermatologia. 2011;86(4 Suppl 1): S168-S172